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**Published**
*With international search report.*

(54) Title: AEROSOL DRUG FORMULATIONS

(57) Abstract

Aerosol formulations suitable for use in pressurised metered dose inhalers comprise a hydrofluoroalkane propellant, a medicament for inhalation and a surfactant which is a $C_8$-$C_{16}$ fatty acid or salt thereof, a bile salt, a phospholipid, or an alkyl saccharide.

The aerosol formulation of the present invention is useful for the local or systemic treatment of diseases and may be administered for example via the upper and lower respiratory tract, including by the nasal route. As such the present invention also provides said aerosol formulation for use in therapy; the use of the aerosol formulation in the manufacture of a medicament for the treatment of diseases via the respiratory tract; and a method for the treatment of a patient in need of therapy, comprising administering to said patient a therapeutically effective amount of the aerosol formulation of the present invention.

The following Examples are intended to illustrate, but not limit, the invention:

Formulations of various medicaments in P134a and/or P227 with different surfactants were prepared in order to assess the quality of the suspensions formed. In the following examples the quality of the suspension is rated as "acceptable" or "good". An acceptable suspension is characterised by one or more of slow settling or separation, ready re-dispersion, little flocculation, and absence of crystallisation or morphology changes, such that the dispersion is sufficiently stable to give a uniform dosing. A good dispersion is even more stable.

Example 1

Micronised formoterol fumarate (1 part) and micronised sodium taurocholate (2 parts) (total 5 mg) were added to a plastic coated glass bottle. The bottle was chilled to approximately -40°C with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a (at approximately -40°C) was added. The bottle was sealed with a metering valve and treated in an ultrasonic bath for about 10 minutes.

A good suspension formed.

Example 2

Micronised budesonide (10 parts)and micronised sodium taurocholate (2 parts) (total 5 mg) were added to a plastic coated glass bottle. The bottle was chilled to approximately -40°C with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a (at approximately -40°C) was added. The bottle was sealed with a metering valve and treated in an ultrasonic bath for about 10 minutes.

A good suspension formed.

Example 3

Micronised salbutamol sulphate (10 parts) and micronised sodium taurocholate (2 parts) (total 5 mg) were added to a plastic coated glass bottle. The bottle was chilled to approximately -40°C with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a (at approximately -40°C) was added. The bottle was sealed with a metering valve and treated in an ultrasonic bath for about 10 minutes.

A good suspension formed.

Example 4

Micronised ipratropium bromide (1 part)and micronised sodium taurocholate (2 parts) (total 5 mg) were added to a plastic coated glass bottle. The bottle was chilled to approximately -40°C with a mixture of carbon dioxide ice and isopropanol, and 10 ml chilled P134a (at approximately -40°C) was added. The bottle was sealed with a metering valve and treated in an ultrasonic bath for about 10 minutes.

A good suspension formed.

Examples 5-8

Examples 1-4 were repeated, substituting propellant P227 for P134a. In all cases, good suspensions formed.

Examples 9-16

Examples 1-8 were repeated with the following addition: ethanol, approximately 650µl, was added to the chilled bottle before sealing with the metering valve. In all cases, acceptable suspensions formed.

Claims

1. A pharmaceutical aerosol formulation comprising a HFA propellant; a physiologically effective amount of a medicament for inhalation; and a surfactant which is a $C_8$-$C_{16}$ fatty acid or salt thereof, a bile salt, a phospholipid, or an alkyl saccharide.

2. A pharmaceutical aerosol formulation as claimed in claim 1, wherein the surfactant is a $C_8$-$C_{16}$ fatty acid salt.

3. A pharmaceutical aerosol formulation as claimed in claim 2, wherein the fatty acid salt is selected from the sodium, potassium and lysine salts of caprylate ($C_8$), caprate ($C_{10}$), laurate ($C_{12}$) and myristate ($C_{14}$).

4. A pharmaceutical aerosol formulation as claimed in claim 1, wherein the surfactant is a trihydroxy bile salt.

5. A pharmaceutical aerosol formulation as claimed in claim 4, wherein the bile salt is selected from the salts of cholic, glycocholic and taurocholic acids.

6. A pharmaceutical aerosol formulation as claimed in claim 5, wherein the bile salt is selected from the sodium and potassium salts of cholic, glycocholic and taurocholic acids.

7. A pharmaceutical aerosol formulation as claimed in claim 6, wherein the bile salt is sodium taurocholate.

8. A pharmaceutical aerosol formulation as claimed in claim 1, wherein the surfactant is a single-chain phospholipid.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/01542

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/12, A61K 47/12, A61K 47/24, A61K 47/26, A61K 47/28
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, WPIL, CLAIMS, EMBASE, CAPLUS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0518600 A1 (SCHERING CORPORATION), 16 December 1992 (16.12.92), page 3, line 24 - line 58, Example X<br>-- | 1-36 |
| A | WO 9111495 A1 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH ET AL), 8 August 1991 (08.08.91)<br>--<br>-------- | 1-36 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 27 March 1996 | 02 -04- 1996 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Anneli Jönsson<br>Telephone No. +46 8 782 25 00 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/01542

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 37
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

05/02/96

International application No.
PCT/SE 95/01542

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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